IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC.,	)	Redacted - Public Version
Plaintiff,	)	[redacted]
v.	)	C.A. No. 18-651-CFC
	)	**ANDA CASE**
TEVA PHARMACEUTICALS USA, INC., et al.	)	**CONSOLIDATED**
Defendants.	)	

DEFENDANTS' RESPONSIVE BRIEF

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I. Vanda failed to show that Defendants will induce infringement of the asserted claims.

A. RE604 Patent Claim 3

Vanda has not shown that Defendants' labels instruct, encourage, or recommend use of Defendants' tasimelteon products to treat Non-24 by "entraining a patient...to a 24 hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours, and maintaining said 24 hour sleep-wake cycle." D.I. 311, Vanda's Opening Brief ("Vanda Op. Br."), 19.

First, Defendants' labels undisputedly do not include the words "entraining," "daily sleep period of approximately 7 to 9 hours," or "target wake time." Tr. 82:1-13 (Court); Tr. 154:21-155:3, 161:12-162:11, 167:2-8 (Polymeropoulos); Tr. 240:23-241:2, 246:7-10 (Combs); Tr. 496:6-11, 514:7-10, 515:7-28 (Winkelman); Tr. 445:12-16 (Jaskot). *Second*, Defendants' labels do not implicitly instruct, encourage, teach, or recommend infringement of this limitation.

Vanda contends that inducement does not require the accused labels to recite the claim language verbatim. Tr. 82:1-84:3; Vanda Op. Br. 19-21. As a general proposition, that is true, but Vanda's cited authority is inapposite here. This is not a case where (i) a claim term is synonymous with a term in the label (*Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1131-32 (Fed. Cir. 2018)); (ii) the Indications and Usage section references a different part of the label that

discusses the claimed method (*Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 645-46 (Fed. Cir. 2017)); or (iii) the label inevitably leads to practicing an infringing method (*AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1058-60 (Fed. Cir. 2010)).

Instead, this case is more like *Grunenthal GmbH v. Alkem Laboratories, Ltd.*, 919 F.3d 1333 (Fed. Cir. 2019). In *Grunenthal*, the patent owner alleged infringement of patented methods of treating "polyneuropathic pain" with tapentadol. *Id.* at 1338. The Federal Circuit affirmed a finding of non-infringement because the defendants' labels did not contain an indication to treat polyneuropathic pain. *Id.* The Court explained that, while both defendants' labels were indicated for severe chronic pain (which included polyneuropathic pain), the proposed labels did not *specifically* encourage treatment of polyneuropathic pain because "even if severe chronic pain includes polyneuropathic pain, it *also* includes mononeuropathic pain and nociceptive pain." *Id*. at 1339 (emphasis added). Moreover, it was "undisputed that neither of the accused ANDA labels list an indication for the management of pain associated with [diabetic peripheral neuropathy ("DPN"), *e.g.*, neuropathic pain]" and that neither of the ANDA labels "mention any DPN clinical studies, which served as the basis for FDA approval of [Plaintiff's drug's] indication for treatment of neuropathic pain." *Id*. at 1339-40. Finally, the court stated the proposed labels "do not implicitly or explicitly

encourage or instruct users to take action that would inevitably lead to use of tapentadol hydrochloride for treatment of polyneuropathic pain." *Id*. at 1340.

1. Defendants' labels will not induce the entrainment limitation.

a) Defendants' labels omit any indication for entrainment.

Just as in *Grunenthal*, where the ANDA labels did not list an indication for the claimed limitation, here it is undisputed that Defendants' labels do not include an entrainment indication. *Id.* at 1339. As discussed below, FDA repeatedly rejected Vanda's attempt to include entrainment in the label. Instead, Hetlioz and Defendants' products are indicated only for the "treatment of Non-24." JTX-30.2; JTX-33.3; Tr. 496:2-5 (Winkelman). And Vanda has presented no evidence that the "treatment of Non-24" indication implicitly instructs users to administer tasimelteon to entrain a Non-24 patient to a 24-hour sleep-wake cycle. *See Grunenthal*, 919 F.3d at 1339.

Vanda argues that, because Non-24 is characterized by a lack of entrainment, a prescriber would understand that treating Non-24 requires entraining the 24-hour sleep-wake cycle and any improvement in Non-24 symptoms are due to entrainment. Vanda Op. Br. 21-22, 25. But as Dr. Winkelman explained, a prescriber can treat the underlying cause of Non-24 (lack of entrainment) *or* can treat its symptoms (sleep disturbances). Tr. 496:6-497:7. In the

case of Non-24, the patients mainly seek treatment because of sleep-disturbance symptoms. Tr. 496:21-23 (Winkelman). And treatment of these sleep disturbances is precisely what Defendants' labels instruct. Tr. 496:18-25, 498:9-16 (Winkelman). As Dr. Winkelman explained, the labels say nothing about entraining a patient's sleep-wake cycle. Tr. 496:6-25, 498:9-16, 501:15-22, 504:19-25.[1]

Also showing that "treatment of Non-24" is not synonymous with "entrainment," Vanda's Clinical Study Report (PTX-815) for the SET study (Study 1 in the labels) differentiates between symptomatic treatment of Non-24 (*i.e.*, sleep endpoints) and treatment of its underlying cause (*i.e.*, entrainment endpoints). PTX-815.19; Tr. 504:19-505:16, 506:7-507:3, 508:3-509:3 (Winkelman). Specifically, in the Primary and Secondary Objectives of the Clinical Study Report, Vanda referred to "*[e]ntrainment* of the 6-sulfatoxymelatonin (aMT6s) rhythm" and "*entrainment* as assessed by urinary cortisol." PTX-815.19 (emphasis added); Tr. 506:7-20, 508:14-18 (Winkelman). Conversely, when discussing sleep endpoints—increased nighttime sleep in the lower quartile of nights ("LQ-nTST") and decreased daytime sleep in the upper quartile of days ("UQ-dTSD")—Vanda

[1] Vanda argues that Dr. Winkelman's testimony is inconsistent with the Hetlioz label's statement that tasimelteon can treat "nighttime sleep disturbances in Smith-Magenis Syndrome." In fact, this language *supports* Defendants' position, because it shows that tasimelteon can treat poor sleep separate and apart from its ability to entrain.

never uses the term "entrainment." PTX-815.19; Tr. 508:3-13, 508:19-509:3 (Winkelman).

b) The clinical-studies sections of Defendants' labels do not disclose entrainment results.

Further, much as in *Grunenthal*, where the ANDA labels did not "mention any DPN clinical studies, which served as the basis for FDA approval" of the claimed limitation, 919 F.3d at 1339-40, here the Clinical Studies sections (§ 14.1) of Defendants' labels do not mention the entrainment endpoints from the clinical studies. Tr. 499:3-22 (Winkelman). Rather, § 14.1 details two sleep-measure outcomes that were assessed in the SET and RESET trials: "duration and timing of nighttime sleep and daytime naps" based on "the 25% of nights with the least nighttime sleep, and the 25% of days with the most daytime nap time." JTX-30.8-9; JTX-33.10-11; Tr. 500:11-501:1 (Winkelman). These endpoints measure the drug's effect on a *symptom* of Non-24: poor sleep. Tr. 499:3-22, 500:11-501:1, 501:9-14, 503:3-504:25 (Winkelman). And they are the same sleep endpoints (LQ-nTST and UQ-dTSD) that Vanda did *not* refer to as entrainment endpoints in the Clinical Study Report.

If tasimelteon invariably treated the cause of Non-24 (*i.e.*, lack of entrainment), as Vanda asserts, one would expect the Clinical Studies section of Defendants' labels to include the entrainment endpoints. Tr. 501:15-22 (Winkelman). But they do not.

Vanda asserts that a prescriber would understand the sleep data in Table 3 "as demonstrating entrainment." Vanda Op. Br. 24. The evidence—including testimony from *both* parties' witnesses—shows otherwise. As Dr. Winkelman testified, the results in Table 3 are "sleep data" and measure only the change in "the symptoms." Tr. 501:9-14. Dr. Polymeropoulos admitted that one *cannot* tell if a patient is entrained solely by looking at sleep duration. Tr. 162:11-21. Inventor Dr. Dressman testified that "just measuring increases in sleep of one hour" would not be called entrainment. Tr. 464:25-465:11. And inventor Dr. Feeney testified that sleep improvement is not necessarily equivalent to entrainment and that one's sleep could improve without entrainment. Tr. 484:9-15.

Vanda's reliance on mention of melatonin acrophase in § 14.1 of Defendants' labels is equally unavailing. Vanda Op. Br. 23. That reference shows only that the individuals *starting* the RESET study were entrained; it does not describe the *outcomes* of either study. Tr. 552:3-18 (Winkelman). Again, the labels present only study data for sleep improvement.

c) No other section of Defendants' labels encourage the use of tasimelteon for entrainment.

Despite Vanda's argument otherwise, neither § 2.2 nor § 2.4 relates to entrainment. *See* JTX-30.2; JTX-33.3. Section 2.2 instructs prescribers to administer tasimelteon one hour before bedtime, at the same time every night, and § 2.4 states that if a patient is unable to take a dose at approximately the same time

on a given night, they should skip that dose and take the next dose as scheduled. *Id*. These instructions were included in Defendants' labels because they reflect the protocol used in the SET and RESET clinical studies that supported Hetlioz's approval. Tr. 550:18-551:10 (Winkelman); PTX-815.37-38. Moreover, a prescriber would understand that tasimelteon induces sleepiness, and thus that one might want to take it near bedtime every night not for entrainment, but for this soporific effect. Tr. 1210:24-1211:6 (Czeisler).

Moreover, contrary to Vanda's assertion, Vanda Op. Br. 22, Dr. Combs never testified that prescribers would understand §§ 2.2 and 2.4 as "preserving the discrete circadian pulse delivered by tasimelteon" needed for entrainment. Nor has Vanda presented any documentary evidence that entrainment is even related to this so-called "discrete circadian pulse." *See also infra* Section II.B. Dr. Combs's speculative testimony is exactly what the Federal Circuit has warned against: "vague label language cannot be combined with speculation about how physicians may act to find inducement." *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 632 (Fed. Cir. 2015).

d) Administration of tasimelteon does not inevitably result in entrainment.

Finally, Vanda does not and cannot argue that entrainment is an *inevitable* result of administering tasimelteon to a Non-24 patient. The results presented in the RE604 patent showed that a substantially larger portion of tasimelteon patients had

improved sleep than were entrained. JTX-1.33 (Tables 1A and 1B); Tr. 509:4-511:5 (Winkelman); Tr. 466:6-22 (Dressman). And, even if tasimelteon entrains some patients, it *also* results in increased sleep, without entrainment, in others, precluding an inducement finding under *Grunenthal*. *See* 919 F.3d at 1339 ("even if severe chronic pain includes polyneuropathic pain, it also includes mononeuropathic pain and nociceptive pain," meaning "the proposed ANDA labels do not specifically encourage" the claimed treatment). That is, there are substantial non-infringing uses for tasimelteon that undercut any inference of intent to induce infringement. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).

2. Vanda's documents show that the labels do not promote entrainment.

Vanda's own draft labels, marketing documents, and FDA communications show that the Hetlioz label, and thus Defendants' labels, do not promote entrainment. Apparently recognizing that these documents are fatal to its inducement claims, Vanda now argues that they are irrelevant. Vanda Op. Br. 25-29. Not so. Vanda's documents are highly relevant: they explain exactly why the labels cannot refer to entrainment, and why "treatment of Non-24" is not synonymous with entrainment.

As to the draft label, Vanda's primary argument is that prescribers will never see that draft label. *Id*. at 26. But Defendants are not relying on the draft label as

evidence of what prescribers would understand. Rather, Defendants are relying on the draft label as evidence of what FDA *prohibited* Vanda from including in the FDA-approved label that prescribers do see—entrainment. As Ms. Jaskot testified, the Indications and Usage, Dosage, and Clinical Studies sections of the draft Hetlioz label included an "extensive discussion of entrainment and circadian regulation." Tr. 419:25-420:10, 445:17-22; JTX-139; *see* Tr. 167:1-8 (Polymeropoulos). However, because FDA did not consider entrainment an appropriate endpoint, Vanda was required to remove all language concerning entrainment, synchronization, and the metabolite aMT6 from the final approved label. *Compare* DTX-139 (draft label), *with* JTX-28 (approved Hetlioz label); Tr. 420:23-422:24 (Jaskot); Tr. 167:1-8 (Polymeropoulos).

Vanda's communications with FDA likewise show that Vanda was *prohibited* from relying on entrainment as evidence that tasimelteon is effective in treating Non-24. As Ms. Jaskot testified, throughout the approval process, Vanda proposed entrainment as an endpoint, but the FDA never agreed. Tr. 401:23-402:7; *see* JTX-66; JTX-68; JTX-69; JTX-67; JTX-110. Further, Vanda's claim that "there was no dispute" between FDA and Vanda that tasimelteon treats Non-24 by entraining the circadian rhythms of patients is wrong. Vanda Op. Br. 27. The FDA rejected every attempt Vanda made to put entrainment in the Hetlioz label. JTX-66.3; JTX-67.1; JTX-68.57; JTX-69.2; JTX-84.9; JTX-110.39; Tr. 402:4-7;

404:13-20, 408:12-409:13, 410:14-411:19, 412:13-413:19, 414:7-16, 417:8-418:4 (Jaskot). The FDA did *not* agree with Vanda that the drug works via entrainment.

To similar effect are Vanda's marketing documents. Tr. 422:25-423:4 (Jaskot). For example, Vanda told its sales force: "ENTRAINMENT SHOULD NOT BE USED TO CONVEY EFFICACY OF HETLIOZ." Tr. 170:11-171:2 (Polymeropoulos); JTX-115.3. Likewise, Vanda instructed its sales force to avoid the terms "entrain," "entrained," and "entrainment," and not to state that tasimelteon "shifted the master body clock." Tr. 171:3-5, 171:19-173:5 (Polymeropoulos); JTX-99.2, 99.4; JTX-115.3, 115.7.

Accordingly, Vanda's documents confirm that defendants' labels do not induce using tasimelteon to entrain.[2]

3. Defendants' labels do not promote or encourage treating Non-24 by entraining the patient such that they have a daily sleep period of approximately 7 to 9 hours.

a) The plain and ordinary meaning of "daily sleep period of approximately 7 to 9 hours"

The crux of the dispute regarding the "daily sleep period" limitation is whether it is simply an "opportunity" for a patient to consolidate her sleep into a 7-9 hour period (Vanda's position) or whether it requires the patient to mostly sleep

[2] The "maintaining said 24 hour sleep-wake cycle" element of claim 3 rises and falls with the "entraining" element. Thus, Defendants' labels do not induce infringement of the former for the same reasons they fail to induce infringement of the latter.

for 7-9 hours (Defendants' position). Defendants' experts explained that the latter interpretation is correct. Tr. 511:23-512:15 (Winkelman); Tr. 802:2-803:6 (Emens). Even Vanda's witnesses, including its CEO, Dr. Polymeropoulos, agreed that a daily sleep period actually requires that the patient fall asleep and then awakens following a normal 7-9 hour period of sleep. JTX-13.543; Tr. 513:19-514:6 (Winkelman); Tr. 489:21-490:12 (Feeney). Further, as Dr. Emens testified, a "sleep opportunity" is a common phrase used in sleep medicine, and if Vanda wanted to use that term it could have—but it did not. Tr. 803:2-803:4; *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (Courts construe claims "as written, not as the patentees with they had written [them]").

In the end, however, Defendants prevail regardless of which definition the Court adopts. As explained below, Vanda failed to present any evidence at trial that Defendants' labels induce infringement of this limitation under either definition. In other words, Defendants' labels do not instruct administration of tasimelteon such that the patient mostly sleeps for 7 to 9 hours or such that the patient has an opportunity to consolidate her sleep into a 7 to 9 hour period.

b) Defendants' labels will not induce the "daily sleep period" limitation.

Defendants' labels say nothing—explicitly or implicitly—about a daily sleep period of 7-9 hours. Vanda's inducement argument on this limitation is fatally flawed.

Vanda points to §§ 1, 2.2, 2.4, and 14.1 of Defendants' labels, which, it asserts, would "encourage prescribers to treat Non-24 by facilitating a daily sleep opportunity of approximately seven to nine hours between a target bedtime and a target wake time." Vanda Op. Br. 33. But these section do not mention "a daily sleep period" (or "a daily sleep opportunity" as Vanda says), much less a daily sleep period of "approximately 7 to 9 hours." Tr. 514:7-10 (Winkelman). Nor do these sections disclose that a patient taking tasimelteon "awakens at or near a target wake time." Tr. 511:13-20, 515:15-18 (Winkelman); Tr. 161:22-162:7 (Polymeropoulos).

Section 1 of the labels states, "Tasimelteon capsules are indicated for the treatment of Non-24 in adults." JTX-030.2; JTX-33.3; Tr. 496:2-5 (Winkelman). Vanda argues that because this section instructs entrainment, it also instructs consolidating sleep into a daily sleep period of 7 to 9 hours. Vanda Op. Br. 33; D.I. 312, Vanda PFF ¶ 150. But, as explained above, the labels do not instruct the use of tasimelteon for entrainment. Tr. 496:6-25 (Winkelman). And, even if they did, Vanda has not cited any documentary evidence that connects entrainment with a daily sleep period of 7 to 9 hours. Rather, Vanda only cites Dr. Combs's conclusory testimony that "because those [§§ 1, 2.4, and the part about the peak melatonin] are going to lead to entrainment, those are going to lead to consolidating your sleep and your nighttime sleep period." Vanda Op. Br. 33.

Notably, Dr. Combs does not refer to the amount of time that should be set aside for consolidating sleep, a key element of the asserted claim (*i.e.*, 7 to 9 hours). At bottom, Vanda's argument here effectively reads the "daily sleep period" term out of the claim: Vanda is attempting to bootstrap its (meritless) argument that Defendants' labels induce entrainment into an argument that they also induce infringement of the separate "daily sleep period" limitation.

Vanda also argues that § 14.1 and Table 3 encourage prescribers to practice the daily-sleep-period limitation. Vanda Op. Br. 33. This argument, too, fails. As Dr. Winkelman explained, § 14.1 does not include information concerning how long patients should set aside for sleep, nor does it include information concerning consolidating sleep into one 7-to-9 hour period. Tr. 515:7-14 (Winkelman); Tr. 161:12-21 (Polymeropoulos). The labels say nothing about even a hope or a goal that Non-24 patients treated with tasimelteon will get 7 to 9 hours of sleep. Tr. 515:19-25 (Winkelman). On the contrary, Table 3 shows that on the worst 25% of nights, patients taking tasimelteon got an average of 4 hours and 5 minutes of sleep. Tr. 500:11-17, 514:23-515:4 (Winkelman); JTX-30.9; JTX-33.11. Four hours and 5 minutes of sleep is certainly not 7 to 9 hours of sleep, nor does it even suggest a sleep opportunity of 7 to 9 hours. Tr. 514:23-515:14 (Winkelman); Tr. 243:19-244:10 (Combs). A patient can hardly awaken at or near a target wake time following a period of 7 to 9 hours if the patient sleeps only for 4 hours.

Finally, Vanda asserts that § 2.2 of Defendants' labels encourages prescribers to establish a target wake time following the 7 to 9 hour sleep period. Vanda Op. Br. 34. But § 2.2 says nothing about a target wake time. JTX-030.2; JTX-33.3; Tr. 515:15-18 (Winkelman); Tr. 161:22-162:7 (Polymeropoulos). Section 2.2 simply instructs that tasimelteon should be taken "one hour before bedtime, at the same time every night." JTX-030.2; JTX-33.3. At best, § 2.2 of the accused labels establishes a target bedtime, *i.e.*, one hour after taking tasimelteon. *Id*. This section says nothing about whether a patient will "*awaken[]* at or near a target wake time *following* a daily sleep period of approximately *7 to 9 hours*," as required by the claim. Tr. 515:15-18 (Winkelman); Tr. 161:22-162:7 (Polymeropoulos); JTX-1.41, claim 1; JTX-030.2; JTX-33.3.

B. '829 Patent Claim 14 and '910 Patent Claim 4

To prove induced infringement, a Hatch-Waxman plaintiff must show "(1) direct infringement and (2) 'that the defendant possessed specific intent to encourage another's infringement.'" *Genentech, Inc. v. Sandoz, Inc.*, 2022 WL 842957, at *5 (D. Del. Mar. 22, 2022) (quoting *Vanda*, 887 F.3d at 1129). Vanda has failed to establish either element.

1. Vanda's DDI patents require (i) discontinuing a CYP1A2 inhibitor or rifampicin and then (ii) treating with tasimelteon—not merely avoiding co-administration of the drugs.

The threshold issue is what the asserted drug-drug interaction ("DDI") claims require. Vanda asserts that claim 14 of the '829 patent and claim 4 of the '910 patent "cover[] not co-administering tasimelteon" with the respectively claimed CYP1A2 inhibitors or the CYP3A4 inducer rifampicin. Vanda Op. Br. 8. But Vanda did *not* draft its claims to broadly cover "not co-administering tasimelteon" with the relevant claimed drug. *Id.* Instead, the asserted claims recite a specific sequence of steps: first, encountering a Non-24 patient who "is being treated" with a specific strong CYP1A2 inhibitor or rifampicin; second, "discontinuing treatment" with the CYP1A2 inhibitor or rifampicin; and third, "treating" the patient with tasimelteon. JTX-4.41 (40:7-15); JTX-3.35 (38:52-60). Defendants' labels do not instruct, encourage, or recommend that prescribers perform this specific series of steps.

2. Vanda failed to prove that prescribers will directly infringe Vanda's DDI patents if the proposed ANDA products are put on the market.

"[D]irect infringement is a necessary predicate for a finding of induced infringement in the usual patent infringement case." *Vanda*, 887 F.3d at 1129. In the Hatch-Waxman context, to establish the predicate act of direct infringement, a plaintiff must prove that "if a particular drug *were* put on the market, it *would*

infringe." *Id.* at 1129-30 (emphasis in original). While the ANDA will "dominate[] the analysis," the direct-infringement question is nevertheless "based on consideration of *all* the relevant evidence." *Id.* at 1130 (emphasis added). Thus, although a patentee need not introduce evidence of "an actual past instance of direct infringement by a physician," the patentee cannot prove inducement if the evidence shows "that an infringing use likely will not occur." *Genentech*, 2022 WL 842957, at *15.

Judge Andrews's recent decision in *Genentech* is instructive. There, the court held that the patentee had not introduced sufficient evidence of direct infringement where the testimony showed that physicians would elect a non-infringing treatment plan over the patented methods. *Id.* at *16. Genentech alleged that Sandoz's generic pirfenidone product would induce infringement of patents that required either co-administering fluvoxamine with pirfenidone or discontinuing fluvoxamine to start pirfenidone treatment. *Id.* at *14. In finding insufficient evidence of direct infringement, the court observed that all the medical experts testified "that in the seven years pirfenidone has been available..., none of them has had a single patient receive fluvoxamine before taking pirfenidone." *Id.* at *16. And the court credited expert testimony that "a physician presented with such a [patient] would likely choose a non-infringing treatment adjustment," like

"choos[ing] something other than [p]irfenidone." *Id.* The same reasoning applies here.

(a) The evidence shows prescribers will not directly infringe the DDI patents.

Just as in *Genentech*, the evidence at trial showed that, as a matter of "real-world practice," physicians will choose a non-infringing treatment rather than "discontinu[e]" a patient's treatment with fluvoxamine, verapamil, ciprofloxacin, or rifampicin to prescribe that patient with tasimelteon. *Id.* at *15 n.9 (citing *Vanda Pharms. Inc. v. Roxane Lab'ys, Inc.*, 203 F. Supp. 3d 412, 433 (D. Del. 2016)); *see Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp.*, 72 F. Supp. 3d 539, 548 (D. Del. 2014). Dr. Winkelman testified that prescribers would not "discontinu[e]" treatment of any of these drugs to give tasimelteon and that it was more likely that physicians will continue treating the patient with the inducer or inhibitor and give the patient a tasimelteon alternative. Tr. 519:13-523:5 (Winkelman); *Genentech*, 2022 WL 842957 at *16. And Dr. Winkelman explained why: The asserted claims cover CYP-inducer/inhibitor drugs that treat serious—sometimes deadly—conditions, and stopping a patient's treatment with any one of these drugs poses serious health risks. Tr. 518:15-519:12 (Winkelman).

- Rifampicin treats "serious and disfiguring bacterial diseases," *id.* 519:12, including tuberculosis, DTX-129.6, leprosy, Tr. 519:7-12 (Winkelman), and Legionnaires' disease, *id.*

- Fluvoxamine is an antipsychotic that treats "severe OCD" and "major depressive disorder." *Id.* 518:18-22.
- Verapamil treats "a variety of heart arrhythmias, coronary artery disease" and a "variety of cardiac issues," *id.* 518:24-519:1, like angina, *id.* 252:18-253:1 (Combs).
- Ciprofloxacin is indicated for treating typhoid fever, infectious diarrhea, DTX-128.5, and the plague, Tr. 252:13-17 (Combs).

See also Tr. 246:23-247:5, 249:21-253:1 (Combs).

Not only do the claimed drugs treat serious conditions, in some cases, discontinuing treatment with them may itself present health risks. Fluvoxamine's label warns "there have been reports of serious discontinuation symptoms" when patients stopped taking the drug, including hypomania, anxiety, and "electric shock sensations." DTX-132.11. And the labels for rifampicin and ciprofloxacin explain that "not completing the full course of therapy [*i.e.*, discontinuing treatment] may...increase the likelihood that bacteria will develop resistance and *will not be treatable* by [rifampicin, ciprofloxacin]...or other antibacterial drugs in the future." DTX-128.42 (emphasis added); DTX-129.9; Tr. 523:2-5 (Winkelman).

(b) There is not a single known instance where a prescriber encountered a Non-24 patient in need of tasimelteon who was already taking one of the claimed inducers or inhibitors.

Another similarity to *Genentech*: the evidence at trial showed there is not a *single known instance* of a prescriber ever encountering a Non-24 patient being

treated with fluvoxamine, verapamil, ciprofloxacin, or rifampicin. *Genentech*, 2022 WL 842957 at *16. That is, the DDI patents claim a treatment scenario that has evidently never happened in the 8 years tasimelteon has been on the market. *Id.* Dr. Winkelman has never heard of such a patient ever being "presented to a physician" in his 30 years as a practitioner. Tr. 494:9-15; 516:5-9. Dr. Combs did not offer any such examples either. *See generally* Tr. 197:19-236:15 (Combs). That the particular situation required for practicing the DDI claims appears never to have occurred is not surprising in view of the rarity of Non-24. *See* Tr. 115:17-116:5 (Polymeropoulos); Tr. 552:20-553:1 (Winkelman).

Given that there is no evidence that the relevant patient required by the claims exists, *there is no evidence that these claims have ever been—or ever will be—practiced*. *See Genentech*, 2022 WL 842957 at *16-17. In fact, Dr. Combs conceded that he never once took a Non-24 patient off any of the claimed CYP-inducers/inhibitor and then gave the patient tasimelteon. Tr. 248:8-249:20 (Combs); *see also* Tr. 516:10-14 (Dr. Winkelman testifying he is not aware of the claims ever being practiced). While Vanda does "not need to prove an actual past instance of direct infringement by a physician to establish" induced infringement, *Vanda*, 887 F.3d at 1129, this evidence is highly relevant to the Court's determination of whether there will be future infringement. *See Genentech*, 2022 WL 842957 at *15; *see also Takeda*, 785 F.3d at 633-35 (finding no direct

infringement based on past conduct, label, and testimony concerning what doctors would do).

Vanda does not dispute this. Instead, Vanda, citing Dr. Polymeropoulos's testimony, states that it "is aware of at least one Non-24 patient who needed both tasimelteon and rifampin." Vanda Op. Br. 12. As an initial matter, there is no evidence how Vanda became "aware" of this or whether Dr. Polymeropoulos has personal knowledge of this incident. Tr. 158:14-20 (Polymeropoulos). Furthermore, Dr. Polymeropoulos did not testify that the individual who received the coincident administration was suffering from Non-24. *Id.* There is *also* no evidence that the patient was *first* receiving rifampicin (which is required to practice the claims). But the most fundamental problem is that the situation Dr. Polymeropoulos described (coincident administration of tasimelteon and rifampicin) is *explicitly excluded* from Vanda's claims.[3] Thus, Vanda's only evidence shows that, on the only known occasion when there may have been an

[3] Dr. Polymeropoulos offered parallel testimony regarding fluvoxamine, which suffers from the same issues as his rifampicin-tasimelteon testimony. Tr. 158:21-159:13 (Polymeropoulos). But there is an additional problem with Dr. Polymeropoulos's fluvoxamine-tasimelteon testimony: he admitted that Vanda does not have any "specific information" about co-administering fluvoxamine and tasimelteon, *id.* 158:21-159:2, and instead simply guessed that this should have occurred because non-24 and OCD are comorbid and fluvoxamine is among the drugs indicated for the latter condition. *Id.* 158:24-159:7.

opportunity to practice a DDI claim, the claim was *not* practiced and a non-infringing treatment regimen was chosen instead.[4]

(c) Dr. Combs's theory that some prescribers would wait for a patient to finish treatment with the claimed drug before administering tasimelteon rests on an untenable reading of the claim.

Vanda's final attempt to show direct infringement violates the claim language. According to Dr. Combs, a physician "would let the[] [patient] finish the course of [treatment with] rifampin[cin]," and "when th[at] course [of treatment] is completed," the physician would "then start tasimelteon." Tr. 247:6-18; *see* Tr. 236:8-17. For starters, that testimony suffers from the same issues as above—namely, there is *no evidence* this scenario ever has or will occur. But Vanda has another problem: that scenario would not infringe the claims.

First, once a patient has completed her treatment with the claimed CYP inhibitor or rifampicin, she is no longer "being treated with a strong CYP1A2 inhibitor [or rifampicin]," as the preambles of the DDI patents require. JTX-3.35 (38:52-60); JTX-4.41 (40:7-15); *see* Tr. 247:6-18 (Combs).

[4] Even had Vanda identified one instance of the claims being practiced, one instance would not be meaningfully probative of how the claims will be practiced in the future. The more probative evidence is the testimony of the parties' clinicians, who have never practiced the claims in the eight years Hetlioz has been on the market.

Second, passively waiting for a course of treatment with rifampicin to finish is not the same thing as actively "discontinuing" rifampicin treatment. The word "discontinue" means interrupting treatment or stopping it short. *See Discontinue*, *Webster's New World College Dictionary* (5th ed. 2016) ("to stop using, doing, etc.; cease; give up"); *Discontinue*, *Webster's New World Dictionary and Thesaurus* (2d ed. 2002) ("[T]o stop; cease; give up."); *Discontinue*, *The Oxford Desk Dictionary* (5th ed. 1995) ("1. come or bring to an end; 2. give up; cease from (doing something)."); *Discontinue*, *The American Heritage Dictionary of the English Language* (3d ed. 1992) ("1. To put a stop to; terminate. 2. To cease trying to accomplish or continue; abandon."); *see also Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, 345 F.3d 1318, 1326 (Fed. Cir. 2003) (relying on common usage dictionary to interpret the "ordinary and customary meaning" of "flex").[5]

Vanda's reading of the claim would lead to absurd consequences: if a patient were on one of the relevant CYP inducers/inhibitor; finished her course of treatment with that drug; and then months or years later were treated with tasimelteon, there would be infringement in Vanda's view. Vanda's overbroad

[5] Vanda's eleventh-hour attempt to read the term 'discontinue' more broadly than its plain and ordinary meaning is particularly improper given that Vanda did not propose this term for construction during *Markman* proceedings and indeed did not even advance this reading in its opening expert reports on infringement. The argument appeared for the first time in Dr. Combs's reply report.

reading cannot be squared with claim requirements of (i) a patient *being treated* with the CYP inducer/inhibitor and (ii) the treatment being *discontinued* (rather than merely running its course).

Because Vanda has failed to show that acts of direct infringement would occur were the ANDA products put on the market, the Court should enter judgement of non-infringement of the '829 and '910 patents.

3. Vanda failed to prove that Defendants specifically intend for physicians to practice the claimed steps of the DDI patents.

Vanda also failed to show that Defendants specifically intend for physicians to "discontinu[e]" a patient's treatment with the covered CYP inducers or inhibitor. Although Defendants' labels state that patients should "avoid use of tasimelteon in combination with...strong CYP1A2 inhibitor [or with rifampicin]," JTX-30.3; JTX-33.4, the labels do not describe how that should be done, let alone state a preference for "discontinuing" treatment with the covered CYP inducers or inhibitors. *See Grunenthal*, 919 F.3d at 1339 (noting that "[t]he pertinent question is whether the proposed label[s] *instruct* users [*i.e.*, physicians] to perform" *all* the claimed steps) (emphasis added).

A generic label's language does not "instruct" the claimed steps of a method patent unless it "specifically directs" that the "particular [claimed] action, or series of [claimed] actions be taken." *Otsuka Pharm. Co., Ltd. v. Torren Pharms. Ltd.,*

Inc., 99 F. Supp. 3d 461, 493 (D.N.J. 2015). A generic label can even "describe" those claimed steps and still fall short of "instructing" them if the label does not require or encourage performing them. *See Shire LLC v. Amneal Pharms., LLC*, 2014 WL 2861430 (D.N.J. June 23, 2014).

(a) Defendants' labels do not instruct "discontinuing" a patient's treatment with fluvoxamine, verapamil, ciprofloxacin, or rifampicin.

Defendants' labels do not instruct, encourage, or recommend the "discontinuing" step claimed in the DDI patents. *HZNP Medicines LLC v. Actavis Lab'ys UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019). Nor do they express a preference for this step. *See AstraZeneca*, 633 F.3d at 1057. The labels do not even *describe* discontinuing treatment with fluvoxamine, verapamil, ciprofloxacin, or rifampicin. *See HZNP*, 940 F.3d at 700. The relevant parts of Defendants' labels are 7.1 and 7.2:

> **7.1 Strong CYP1A2 Inhibitors (e.g., fluvoxamine)**
>
> Avoid use of tasimelteon in combination with fluvoxamine or other strong CYP1A2 inhibitors because of a potentially large increase in tasimelteon exposure and greater risk of adverse reactions.
>
> **7.2 Strong CYP3A4 Inducers (e.g., rifampin)**
>
> Avoid use of tasimelteon in combination with rifampin or other CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy.

JTX-30.3; JTX-33.4.

These sections amount to warnings against *co-administering* tasimelteon with the covered CYP-inducers/inhibitor. But, as Dr. Winkelman explained, the labels leave it to prescribers how to implement this warning. Tr. 517:12-518:14 (Winkelman). Never once do the labels state that treatment with CYP inducers/inhibitors should be *discontinued*—as required by the claims—so that treatment with tasimelteon can occur.

As a matter of ordinary English usage, a warning to avoid taking a drug while pregnant or nursing is not an instruction to discontinue being pregnant or discontinue nursing. Similarly, a warning to avoid taking two drugs together is not an instruction to discontinue whichever one of the drugs the patient is already taking. Indeed, that kind of warning is not an instruction at all. *See, e.g.*, *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, at *18 (D.N.J. Aug. 29, 2014) ("[T]here is a rather significant difference between a warning and an instruction. A warning provides information regarding potential risk. It does not prescribe a course of action.").

Even Dr. Combs, when asked whether the label instructs physicians to "discontinue rifampicin and put that patient on tasimelteon," volunteered that the label "doesn't say anything about stopping it totally." Tr. 247:6-18 (Combs). He instead testified again that physicians will advise patients to let the rifampicin treatment run its course. *Id.* But, as discussed above, that is not infringement.

The Federal Circuit has, on similar facts, held that an open-ended warning is not an instruction for prescribers to take a specific action. In *HZNP*, the Court held that the defendants' generic labels for a topical ointment did not instruct users to perform a three-step method patent that claimed (1) applying the ointment to the knee, (2) waiting for the knee to dry, and (3) applying "sunscreen, insect repellant, or a second topical medication" to the knee. 940 F.3d at 702. The labels explicitly instructed the reader to perform the first two steps, and the third step was described in a warning section of the label, which cautioned readers to "[w]ait until the treated area is dry before applying sunscreen, insect repellant...or other topical medication to the same knee you have just treated." *Id.* at 700. Because this warning merely mentioned but "d[id] not require subsequent application of sunscreen, insect repellant, or a second medication," it did not instruct users to perform this claimed step. *Id.* at 702.

Because defendants' labels do not require, express a preference for, or even explicitly describe discontinuing a patient's treatment with the covered CYP-inducers/inhibitor, Vanda cannot show any intent to induce infringement. *Id.*

Lastly, Vanda's assertion that Dr. Winkelman "agreed that the Defendants' labels explicitly contemplate prescribers performing that infringing method" is incorrect. Vanda Op. Br. 17. Dr. Winkelman did not testify that the labels "explicitly contemplate" infringement. *See* Tr. 547:7-16 (Winkelman). Moreover,

"contemplating" infringement is not the test. *Takeda*, 785 F.3d at 631 ("Merely 'describing' an infringing mode is not the same as 'recommending,' 'encouraging,' or 'promoting,' an infringing use, or suggesting that an infringing use 'should' be performed.") (cleaned up). When asked to apply the correct legal test, Dr. Winkelman consistently maintained that the labels do not promote infringement. Tr. 546:16-21; 547:7-12 (Winkelman).

Vanda also incorrectly states that Dr. Winkelman "agreed [with Dr. Combs] that it is a reasonable reading of the [defendants'] label[s] that physicians will discontinue fluvoxamine treatment, and switch the patient to another anti-psychotic." Vanda Op. Br. 10. Dr. Winkelman said the opposite: "That is an option. *That's not something a doctor would do.*" Tr. 547:20-548:8 (emphasis added).

(b) A label that is indifferent between infringing and noninfringing options does not induce infringement.

Relying principally on *AstraZeneca*, Vanda argues that induced infringement occurs if a label teaches several treatment options, so long as one infringes. Vanda misstates the law, and its reliance on *AstraZeneca* is misplaced.

The defendants' labels do not "teach" multiple options; they state that one should avoid co-administration, leaving it to prescribers to determine how best, if at all, to do so. Nevertheless, Vanda argues (at 13-18) that there are essentially two ways to comply with the warning on the label: (i) discontinue taking the CYP

inhibitor or rifampicin or (ii) refrain from taking tasimelteon. According to Vanda, because some prescribing physicians are likely to choose the first option rather than the second, the label induces infringement. But a label that is indifferent as between infringing and noninfringing uses does not induce infringement. That is because a physician might follow such a label and never infringe.

Shire is instructive on this point. There, the asserted claims included a step of administering an ADHD medication "with...food," but the accused label stated that the generic drug "may be taken '*with* or without food.'" 2014 WL 2861430, at *4-5 (emphasis added). Providing two options, only one of which was infringing, was not enough to show the defendants specifically intended to induce infringement. *Id.* As the district court explained, "the statement that the medication may be taken with or without food...is indifferent to which option is selected." *Id.* at *5. The labels therefore could not "be reasonably understood to be an instruction to engage in an infringing use." *Id.*

The same finding necessarily follows here. Defendants' labels do not "instruct" physicians to discontinue a patient's treatment of fluvoxamine, verapamil, ciprofloxacin, or rifampicin by warning to avoid coadministering them with tasimelteon, for there are non-infringing ways to heed that warning. *See id.*; *see also Takeda,* 785 F.3d at 635 ("Speculation or even proof that some, or even many, doctors would [directly infringe]...is hardly evidence of inevitability. This

evidence does not show anything more than that there may be some infringing uses."); *HZNP*, 940 F.3d at 702 ("[Plaintiff's] evidence...establishes that some users might infringe. Th[at] evidence, however, does not establish that 'the proposed label instructs users to perform the patented method.'").[6]

AstraZeneca does not apply here. The asserted patents in that case claimed a method of administering an asthma drug "once per day." The Federal Circuit held that the generic label encouraged prescribers to infringe because the label urged physicians to perform a series of steps that "necessarily le[d]" to practicing the "once per day" limitation. *Takeda*, 785 F.3d at 634 (distinguishing *AstraZeneca*). Specifically, while the label instructed physicians to administer the drug as a 0.5 mg dose twice a day, it also told physicians it was "desirable" to "downward-titrate" the drug to the "lowest effective dose." *AstraZeneca*, 633 F.3d at 1057. Because the label stated that the "lowest effective dose" was 0.25 mg, "titrating down [to that dose] *required*...taking it once a day." *Takeda*, 785 F.3d at 634 (emphasis added). The label therefore encouraged physicians to take steps that inevitably resulted in performing the claimed method of treatment.

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[6] *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*, 7 F.4th 1320 (Fed. Cir. 2021), is not to the contrary. There the label encouraged *both* an infringing use (in patients with congestive heart failure) *and also* a non-infringing use. In contrast, here (as in *Shire*), the label does not specifically encourage either the infringing use or the non-infringing use: "Avoid coadministration," the label says, without saying how to do so—and so without encouraging the specific steps needed for infringement.

Here, Vanda cannot point to any language in Defendants' labels that describe—let alone encourage—steps that invariably lead to "discontinuing" a patient's treatment with fluvoxamine, verapamil, ciprofloxacin, or rifampicin. Again, the only parts of Defendants labels that even mention these drugs are 7.1 and 7.2, which simply warn physicians not to co-administer the drugs with tasimelteon. JTX-30.3; JTX-33.4. Physicians can follow this warning *without* "discontinuing" a patient's treatment with any of the covered CYP inducers or inhibitors. Tr. 519:13-523:5 (Winkelman). There is therefore no evidence that infringement would inevitably occur—in all patients or any subset of patients—if a prescriber followed the instructions of the labels. Indeed, the evidence is strongly to the contrary: Hetlioz has been on the market for *eight years* and there is no evidence that these claims have ever been practiced.

II. Vanda's evidence of secondary considerations is weak and cannot overcome Defendants' strong showing of obviousness.

Vanda, apparently unhappy with the validity case it put on at trial, has manufactured a brand-new one for purposes of post-trial briefing. Vanda asserts (at 35-46) that four separate secondary considerations of non-obviousness—unexpected results, long-felt need, industry praise, and failure of others—support the validity of its claims. The bulk of these arguments are nowhere to be found in Vanda's trial presentation. For example, while Vanda spends several pages arguing unexpected results, *see* Vanda Op. Br. 37-42; Vanda PFF ¶¶ 167-191, its invalidity

experts uttered the word "unexpected" a collective total of one time: when Dr. Czeisler said that, if Vanda's Phase III trial had failed, "it would not have been unexpected." Tr. 1183:25-1184:4. Some of Vanda's present arguments are not even in Vanda's expert reports. For example, Vanda has never argued—not once—that the DDI patents produced unexpected results.

The likely reason that Vanda did not previously focus on these arguments is simple: they are exceedingly weak. Vanda has failed to show that its evidence of secondary considerations has the required nexus to the specific claimed inventions (as opposed to knowledge already in the prior art). And, even if Vanda had shown a nexus, the evidence would be woefully insufficient to overcome Defendants' strong showing of obviousness. *See generally* D.I. 313, Defs.' Op. Br.; D.I. 314, Defs.' PFF; *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1376-77 (Fed. Cir. 2022) (finding evidence of secondary considerations, even if credited, "not sufficient to overcome the strong case of obviousness").

A. Vanda has failed to show that the purported secondary considerations of non-obviousness have a nexus to the claimed inventions.

As Vanda acknowledges, it bears the burden of demonstrating nexus, *i.e.*, that the alleged evidence of objective indicia are "the 'direct result of the unique characteristics of the claimed invention[s].'" Vanda Op. Br. 35-36 (citations omitted); *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir.

2019). Vanda failed to meet this burden. Despite presenting eleven witnesses, Vanda failed to ask a single question regarding nexus. This did not go unnoticed by the Court, which, after the close of evidence, questioned whether there was evidence of nexus. Tr. 1222:12-1224:24.

In its two-paragraph section on evidence of an alleged nexus, Vanda argues that its "research...revealed" evidence of objective indicia and that "FDA relied on" Vanda's data. Vanda Op. Br. 35-36. Vanda vaguely states that "[t]he patents flow directly from these observations" and "claim[] methods that resulted in these observations." *Id*. at 36. Neither assertion is relevant under the law. It is insufficient for the patentee to merely assert that its patents "flow" from observations and claim methods that "result" in observations. Instead, the objective indicia must be the "direct result of the unique characteristics of the" asserted claims. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019).

Rather than being tied to the asserted claims, the evidence Vanda relies on relates generally to tasimelteon as a compound or as a treatment. But Vanda did not invent tasimelteon or using tasimelteon to treat circadian rhythm disorders. Tr. 191:8-11, 258:14-15, 595:7-17, 724:13-725:2. Those things were invented by Bristol Myers Squibb ("BMS") and claimed in BMS's U.S. Patent No. 5,856,529. Tr. 191:8-11, 258:14-15, 595:7-17, 613:15-614:2, 614:16-18, 1010:9-16. Vanda fails to show that any evidence of alleged objective indicia is a direct result of one

of the claimed inventions, rather than BMS's invention of tasimelteon (and its use as a circadian-rhythm-disorder treatment).

BMS's '529 patent has another important implication—it serves as a blocking patent. Vanda does not even mention BMS's '529 patent in its briefing, despite the Court having noted the blocking-patent issue. Tr. 1222:1-11. The existence of a blocking patent can negate a finding of nexus between evidence of objective indicia and the claimed invention. *See Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.,* 903 F.3d 1310, 1337-42 (Fed. Cir. 2018); *Allergan, Inc. v. Teva Pharms. USA, Inc.*, 2017 WL 4803941, at *49 (E.D. Tex. Oct. 16, 2017) (Bryson, J.), *aff'd*, 742 F.App'x 511 (Fed. Cir. 2018). The Federal Circuit has held that a blocking patent's "potential deterrent effect is relevant to understanding why others had not made, developed, or marketed that 'blocked' invention and, hence, to evaluating objective indicia of the obviousness of the later patent." *Acorda*, 903 F.3d at 1338. Here, Vanda admits that the '529 patent "would cover the use of tasimelteon for anything." Tr. 1222:9-10. The only company with a license from BMS for this blocking patent has been Vanda. Tr. 190:3-11. As long as the '529 patent is in force, no one else can sell any tasimelteon product, regardless of how obvious it would be to do so. Tr. 190:18-191:5; 1010:9-16.[7]

[7] Vanda has not argued it is entitled to a presumption of nexus here, and for good reason: Vanda has not shown that Hetlioz is "coextensive" with the claims.

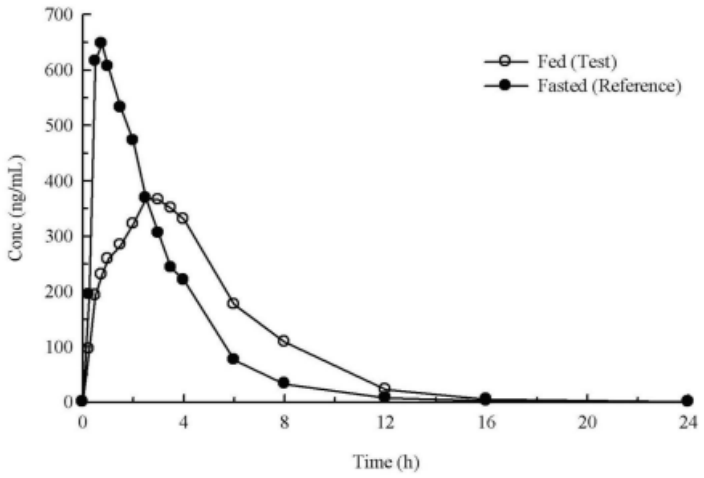
B. Vanda's evidence of secondary considerations is weak on the merits.

None of Vanda's four proffered secondary considerations is probative of non-obviousness.

As an initial matter, Vanda's assertions that a "short, sharp pulse" of tasimelteon is needed to effectively treat Non-24, *e.g.*, Vanda Op. Br. 2, 36-37, 41, are unsupported. None of the documents Vanda cites remotely supports this claim. The clinical study reports on which Vanda relies (JTX-58.47, 60; PTX-187.7-8, 56; PTX-185.10, 70) say nothing about a "short, sharp pulse" being necessary for efficacy. For example, JTX-58.47, which Vanda repeatedly cites (without additional explanation), merely depicts graphs of tasimelteon pharmacokinetics:

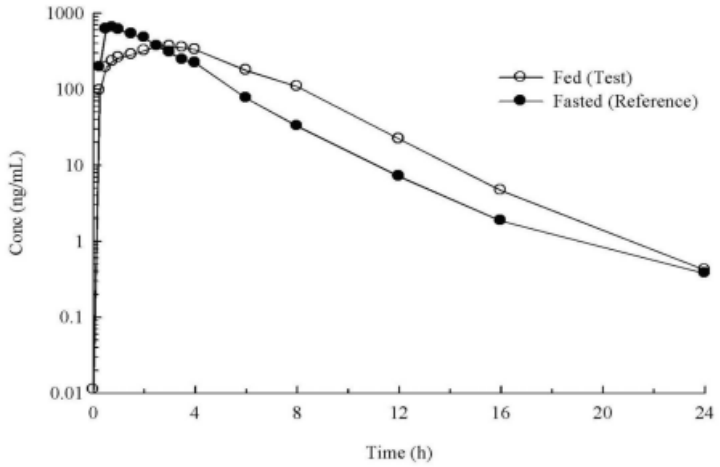
See Teva Pharms. Int'l GmbH v. Eli Lilly & Co., 8 F.4th 1349, 1360 (Fed. Cir. 2021). Even if Vanda were entitled to a presumption of nexus, however, the presence of the blocking patent would be sufficient to rebut it.

Figure 2: Mean Plasma Concentrations of VEC-162 after Single Oral 100 mg Doses Under Fasted and Fed Conditions (linear axes)



Source: *Summary 16.2.6.1.1*

Figure 3: Mean Plasma Concentrations of VEC-162 after Single Oral 100 mg Doses Under Fasted and Fed Conditions (semi-logarithmic axes)



JTX-58.47. Vanda also cites JTX-110.139, which is a page out of the briefing materials from the FDA's advisory committee meeting regarding tasimelteon. *See* Vanda Op. Br. 2, 37. This page does not draw any connection between tasimelteon's pharmacokinetic profile and its efficacy either.

Nor do the passages of the patents cited by Vanda say anything about a "short, sharp pulse" being necessary for efficacy. JTX-1.24 (3:21-31) recites the

administration protocol claimed in the RE604 patent, and JTX-3.33 (33:65-67), JTX-4.35 (27:54-62), JTX-5.3 (2:55-62) simply describe the pharmacokinetic results of Vanda's studies of tasimelteon's interaction with CYP1A2 inhibitors, CYP3A4 inducers, and food, respectively.

What Vanda does *not* cite is any documentary evidence that actually connects tasimelteon's pharmacokinetic profile—*i.e.*, the shape of the graphs in the clinical study reports—to tasimelteon's efficacy in treating Non-24. Instead, Vanda relies exclusively on the self-serving testimony of its CEO and a passing remark from Dr. Czeisler. Vanda Op. Br. 2, 36-37. These unsupported arguments about the "short, sharp pulse" purportedly necessary for tasimelteon efficacy should therefore be given no weight.

1. The purported inventions claimed in the asserted patents did not produce unexpected results.

(a) RE604 patent

Vanda's unexpected-results arguments on the RE604 patent are meritless.

i. Half-life. Vanda's argument that tasimelteon's longer half-life relative to melatonin "would have led one of skill not to expect that tasimelteon would work for treating Non-24," Vanda Op. Br. 38, is incorrect. Tasimelteon's longer half-life was known in the prior art and was cited as an *advantage* over melatonin. Hardeland, for example, noted in 2009 that "a major disadvantage of melatonin is its short $t_{1/2}$ in the circulation," which prompted pharmaceutical companies to

develop melatonin agonists with longer half-lives like ramelteon and tasimelteon. DTX-16.2.

Vanda asserts that tasimelteon's longer half-life would have made a skilled artisan worry about "spillover"—the prospect that the tasimelteon would remain in a patient's system long enough to cause an (unhelpful) phase advance in addition to the (helpful) phase delay. Vanda Op. Br. 38. But, as Defendants' expert Dr. Emens—whom the Court found "very credible" and lacking "any source of bias," Tr. 1258:2-11—explained, skilled artisans had already concluded before January 2012 that 20 mg of tasimelteon (and higher doses as well) were effective at treating sleep disorders. Tr. 882:20-883:22 (Emens). Accordingly, whatever spillover 20 mg caused, it was not enough spillover to impair tasimelteon's efficacy. *See id.* Tellingly, Vanda's expert Dr. Czeisler admitted that he was not aware of a *single* prior-art reference expressing any concern about a potential spillover effect with tasimelteon. Tr. 1199:2-6 (Czeisler). Vanda's spillover arguments amount to a post-hoc attempt to explain why a skilled artisan's reasonable expectation of success might have been wrong. *See* Tr. 882:20-883:22 (Emens).

ii. Dose. Vanda asserts that "[n]o one would have thought 20 mg was the right dose." Vanda Op. Br. 38. Well, no one, except:

- Hardeland ("The most effective doses of tasimelteon were in the range of 20 to 50 mg/day." DTX-16.7);

- Lankford ("There is an ongoing Phase III trial of tasimelteon in blind people with no light perception and with non-24 hour sleep-wake disorder...designed to assess the effectiveness of 20 mg tasimelteon...." DTX-20.6); and
- *Vanda itself* ("An oral dose of about 20 to about 50 mg is effective in treating sleep disorders." DTX-41.24 ('244 publication)).

Indeed, five years before the priority date, Vanda actually *wrote patent claims*—claims published in the prior art—directed specifically to the treatment of circadian rhythm sleep disorders with 20 to 50 mg tasimelteon administered 0.5 hours before bedtime. DTX-41.25 (claims 1, 4, 5, 8); *see* Tr. 727:23-728:6 (Emens). Vanda's litigation-driven argument that the 20-mg dose was unexpected is contradicted by Vanda's own prior-art statements.

Moreover, before the priority date, skilled artisans knew that Vanda was running a Phase III trial that involved administering 20 mg tasimelteon to Non-24 patients one hour before bedtime. *See* DTX-42.9-10; Tr. 796:24-797:12 (Emens); DTX-20.6. Vanda's unexpected-results argument thus amounts to an assertion that Vanda invested enormous resources into a Phase III trial but inexplicably designed the protocol to use a dose and timing of administration that "[n]o one would have thought" would work. Vanda Op. Br. 38. That is not a credible argument.

The results of the Rajaratnam paper would have reinforced, rather than undermined, a skilled artisan's reasonable expectation of success that the 20-mg

dose would work. *Contra* Vanda Op. Br. 38. The Rajaratnam study involved patients who underwent a "dramatic[]" five-hour phase advance, which would "model...something like jet lag from New York to London." Tr. 885:9-886:1 (Emens). Rajaratnam found that, in that model, only the 100-mg dose achieved a phase advance statistically different from placebo. PTX-816.7-8. But, as Dr. Emens explained, the 20-mg dose achieved a phase-shift that, while not statistically different from placebo, still exceeded one hour, *see* PTX-816.7 (Fig. 2.C), which would have been more than sufficient to treat Non-24. Tr. 885:16-19 (Emens).

Perhaps the best evidence that Rajaratnam would have reinforced a skilled artisan's expectation of success is Vanda's own '244 publication, which, *after reviewing the Rajaratnam results*, concluded that 20 mg was "preferable to an oral dose of about 100 mg" and that "[a]n oral dose of about 20 to about 50 mg is effective in treating sleep disorders." DTX-41.24. And, as Dr. Emens explained, a skilled artisan would not have looked at Rajaratnam "in isolation. I know from Rajaratnam, hey, I can get a 20-milligram phase shift, and I know from clinical trials that that's actually what they chose in their clinical trial of Non-24." Tr. 885:20-24.

Finally, Dr. Emens' 2017 statement that "[i]t is conceivable that the 20-mg dose was too large," Vanda Op. Br. 38 (quoting PTX-5.9-10), is not probative of

non-obviousness for two reasons. *First*, a 2017 paper provides no evidence about what skilled artisans would have expected in January 2012. *See Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019) (to be probative of non-obviousness, "the results must be 'unexpected by one of ordinary skill in the art *at the time of the application*'") (emphasis added). *Second*, the passage Vanda quotes in fact confirms that 20 mg tasimelteon *is effective* at treating Non-24 (albeit arguably less effective than melatonin) and simply hypothesizes that a lower dose might be *better*. *See* PTX-5.8. Even if made before the priority date, such statements would have confirmed a reasonable expectation of success—not undermined it.

iii. Timing of administration. Vanda's litigation-driven argument that "[i]t was unexpected that success could be obtained administering tasimelteon before bedtime," Vanda Op. Br. 39, is once again contradicted by Vanda's own prior-art statements. Vanda stated in the '244 publication that tasimelteon should be administered "about 1/2 hour before sleep time," DTX-41.24; *see also* DTX41.25-26, and Vanda's prior-art clinical trial protocol instructed that tasimelteon should be administered one hour before bedtime, *see* DTX-42.9-10. Indeed, *every piece of tasimelteon prior art* Defendants have relied on describes administering the drug shortly before bedtime. *See* DTX-20.5 (Lankford); DTX-41.10 ('244 publication); DTX-16.5-6 (Hardeland); Tr. 807:13-808:20, 812:24-

813:9 (Emens). Moreover, as Dr. Czeisler admitted, tasimelteon's known soporific properties would have provided an additional reason for skilled artisans to administer tasimelteon shortly before bedtime. Tr. 1211:2-6 (Czeisler). There was nothing remotely unexpected about the claimed timing of administration.

iv. Phase-response curve. Vanda's arguments about the phase-response curve, Vanda Op. Br. 38, likewise fail. The lack of a phase-response curve for tasimelteon is irrelevant given that—as just explained—long before January 2012, the prior art uniformly described tasimelteon administration as occurring shortly before bedtime.

* * *

In short, Vanda's unexpected-results arguments are not supported by—and in many cases flatly contradict—the record evidence. Moreover, even if Vanda had shown that tasimelteon proved better at treating non-24 than skilled artisans expected as of January 2012—and it has not—the difference was at best "only one of degree, and not one of kind." *Lovell Mfg. Co. v. Cary*, 147 U.S. 623, 633 (1893); *see Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (unexpected results must be "different in kind and not merely in degree from the results of the prior art"). Vanda's evidence thus does not overcome Defendants' strong showing of obviousness.

(b) ’487 patent

Vanda has not shown that the invention claimed in the ’487 patent produced unexpected results.

As an initial matter, the premise of Vanda’s argument—that “administration of tasimelteon with food...decrease[s] its efficacy in treating Non-24,” Vanda Op. Br. 40—is unsupported. As Dr. Emens explained, the ’487 patent specification discusses only “the effects of administering tasimelteon to sighted healthy individuals with or without food.” Tr. 826:14-18. And, while the ’487 patent incorporates the specification of the RE604 patent, that patent likewise does not provide any evidence that tasimelteon is more effective at treating Non-24 when administered without food. Instead, it contains the results of the SET and RESET studies, which at no point compared the effects of administering tasimelteon with food and without food. *See* Tr. 827:11-18 (Emens). Dr. Emens explained that, “to figure out [if] tasimelteon is more effective at treating Non-24 when administered without food than [when] it is administered with food,” one would “have to do a head-to-head trial…where you gave the tasimelteon to a group of patients with Non-24 with food and have some matched patients or crossover to the same patents where you then give it with and without food and see if one is more likely to cause treatment success than the other.” Tr. 827:19-828:3. Because Vanda has performed

no such study, its assertion that administering tasimelteon without food is better at treating Non-24 is unsupported attorney argument.

Vanda notes that, in 2017, Dr. Emens hypothesized that administration of tasimelteon with food "might be *helpful*" because it could allow tasimelteon to be taken earlier than one hour before bedtime. Vanda Op. Br. 40 (citing PTX-5.9). That proves Defendants' point. Skilled artisans do not yet know whether tasimelteon should optimally be taken with or without food to treat Non-24. That is why, in 2017 (years after the priority date), experts like Dr. Emens were still debating the issue.

Moreover, even if there were evidence that administering tasimelteon without food is more effective at treating Non-24 than administering it with food, that still would not be probative of non-obviousness because Vanda has not shown that such a result was *unexpected*. Vanda presented no evidence of what a skilled artisan *would have expected* as of January 2012 vis-à-vis the administration of tasimelteon with versus without food. That means there is no baseline against which to assess Vanda's claim of unexpected results. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (noting that, "in order to properly evaluate whether a superior property was unexpected," a court must "consider[] what properties were expected," and rejecting unexpected-results argument

because patentee had not presented "*any* evidence of what the skilled artisan would have expected").

(c) '910 patent

Vanda has likewise not shown that the invention claimed in the '910 patent produced unexpected results.

Vanda notes that, based on BMS's initial in vitro work with tasimelteon—summarized in Vachharajani—the authors concluded that "[n]o metabolism of [tasimelteon] was observed following incubation with...CYP3A4." Vanda Op. Br. 40-41 (quoting JTX-91.10). But, as Dr. Greenblatt explained, a skilled artisan aware of that disclosure would not have "exclude[d] a major role of CYP3A4 in the induced state." Tr. 1116:13-20. That is because "induction causes a massive increase in the amount of enzymes," meaning "you can't exclude a major role of CYP3A4 in the induced state even if you can't detect it in the uninduced state." *Id.* A skilled artisan would have been particularly likely to suspect a potential interaction between tasimelteon and strong CYP3A4 inducers given the knowledge in the art that (i) the structurally analogous compound ramelteon exhibited a "large" drug-drug interaction with strong CYP3A4 inhibitors, Tr. 1116:21-1117:13 (Greenblatt), and (ii) CYP3A4 resides in the gastrointestinal tract, is the "most abundant" enzyme in the liver, and metabolizes a large percentage of drugs, *see* Tr. 1050:20-1052:2 (Greenblatt); Tr. 1146:19-25 (Parkinson).

(d) ’829 patent

Vanda has not shown that the invention claimed in the ’829 patent produced unexpected results either. On the contrary, the interaction between tasimelteon and strong CYP1A2 inhibitors was decidedly expected.

Hardeland, for example, expressly discloses that “tasimelteon was primarily metabolized by the CYP1A2...isoenzyme[].” DTX-16.4 (citing Vachharajani); Tr. 1036:3-16, 1049:3-25, 1100:2-9 (Greenblatt). Hardeland further states that because “tasimelteon is metabolized by the CYP isoenzymes 1A2...*coadministration of any drug that inhibits one of these isoenzymes should be regarded with caution*.” DTX-16.6 (emphasis added); *see* Tr. 1049:3-1050:9, 1067:17-20, 1069:7-22 (Greenblatt). A skilled artisan would have expected a drug-drug interaction between tasimelteon and strong CYP1A2 inhibitors for the additional reason that ramelteon was known to have a large drug-drug interaction with strong CYP1A2 inhibitors, such that co-administration of ramelteon and strong CYP1A2 inhibitors was contraindicated. *See* Tr. 1037:5-6, 1038:25-1039:6, 1040:6-23, 1043:18-1046:3, 1116:24-1117:13 (Greenblatt); Tr. 1156:6-10 (Parkinson); JTX-93.4; DTX-16.2; JTX-35.2, 35.8, 35.10; JTX-92.1; DTX-28.9.

Vanda’s argument boils down to an observation that a skilled artisan would not have known *with certainty* whether co-administration of tasimelteon and strong CYP1A2 inhibitors should be avoided without performing an in vivo test. Vanda

Op. Br. 41-42. True—but irrelevant. That skilled artisans are not *absolutely sure* of the outcome of a study in advance does not render the result of that study unexpected. *Cf. Pfizer*, 480 F.3d at 1364 ("the expectation of success need only be reasonable, not absolute").

2. The purported inventions did not fulfill a long-felt or unmet need.

Contrary to Vanda's argument, as of January 2012 there was no "long-felt, unmet need for a safe and effective treatment for Non-24," Vanda Op. Br. 42.

As Dr. Emens explained, by 2003—and certainly before 2012—the prior art contained unequivocal evidence that melatonin is effective at treating Non-24. JTX-146 (Hack 2003); *see* Tr. 716:2-721:4 (Emens). The data were "clear": "melatonin could effectively entrain the circadian pacemaker and improve sleep...in blind individuals with Non-24." Tr. 1217:14-17 (Emens). Indeed, the data were so clear that, in 2007, "[t]he American Academy of Sleep Medicine issued two sets of practice parameters using two separate task forces and reached the same conclusion that that was the effective treatment for Non-24. And that was what was being recommended to sleep physicians in this country." Tr. 1217:18-23 (Emens). Thus, to the extent there was at some point a need for an effective Non-24 treatment, melatonin satisfied it long before January 2012. *See Nike, Inc. v. Adidas AG*, 955 F.3d 45, 55 (Fed. Cir. 2020) (rejecting argument that invention satisfied long-felt need because other prior art satisfied the allegedly unmet need).

More generally, the fact that melatonin is not successful in treating 100% of Non-24 patients, *see* Vanda Op. Br. 42-43, does not indicate that there was a long-felt or unmet need for an effective treatment for Non-24. By that logic, there is *still* a long-felt and unmet need, because tasimelteon is not 100% effective in treating Non-24 either. *See* JTX-5.8. Indeed, the available evidence suggests that tasimelteon may in fact be *less effective* than melatonin. *See id.* (noting that the "entrainment rates for tasimelteon are a little lower than those for melatonin administered for 3-12 weeks" and that "[t]he true comparative efficacy of melatonin and tasimelteon for entrainment in non-24 awaits well-designed head-to-head trials"); *see also* Tr. 1217:24-1218:20 (Emens) (noting that the "lowest estimate" of the percentage of Non-24 patients melatonin entrains is about 60%); *cf. Spectrum Pharms., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1336 (Fed. Cir. 2015) (rejecting patentee's arguments that claimed "substantially pure" form of compound met a long-felt need because the substantially pure form was "clinically interchangeable" with the form of the compound available in the prior art).[8]

[8] That melatonin is not FDA approved to treat Non-24, *see* Vanda PFF ¶¶ 202-204, is irrelevant to non-obviousness. The asserted claims do not require FDA approval. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010) (evidence of long-felt need is irrelevant to non-obviousness if feature that purportedly satisfies the need is not claimed).

3. The purported inventions have not received significant industry praise.

Vanda's evidence of industry praise, *see* Vanda Op. Br. 44, is at best weak and at worst irrelevant. That an FDA reviewer described the "design of the SET and RESET trials" as "very novel [and] unique," Vanda Op. Br. 44 (quoting JTX-84.7), is irrelevant; the asserted patents claim a method of treating patients, not a study design. And that Vanda has received some measure of praise for its development of Hetlioz generally does not indicate that the *claimed methods of treatment* have been praised. This evidence is therefore not probative of non-obviousness either. *See Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020) (finding evidence of industry praise not probative of non-obviousness because praise was not directed specifically "to the claimed method").

4. Vanda has not presented probative evidence of failures of others.

Vanda presents three arguments in support of its contention that "others failed to develop [the] claimed invention." Vanda Op. Br. 44. All three lack merit.

First, Vanda contends that the "melatonin researchers" failed to demonstrate that melatonin can effectively entrain the circadian rhythms of Non-24 patients "in a large scale study." Vanda Op. Br. 45. That is irrelevant. As explained above, the prior art showed *unequivocally* that melatonin could successfully entrain patients with Non-24. *See supra* Section II.B.2; Defs.' Op. Br. 3-6. Even without "a large

scale study," there was zero dispute that melatonin worked. The fact that it "took over 12 years before even one patient was successfully entrained using melatonin," Vanda Op. Br. 45, is beside the point; melatonin's success in Non-24 had been shown by 2000, more than a decade before the priority date. And Vanda's assertion that there was somehow a failure of others because "no one has ever entrained a patient using 20mg of melatonin," *id.*, is absurd. Skilled artisans knew the effective dose ranges of melatonin by the early 2000s. The fact that the effective dose of tasimelteon—a different compound—turned out to be higher than the effective dose of melatonin is irrelevant to whether melatonin was successful in treating Non-24. *See* Tr. 833:13-834:21 (Emens).

Second, Vanda states that "BMS failed to develop any successful treatment using tasimelteon, at any dosage for any disease." Vanda Op. Br. 45. But Dr. Polymeropoulos admitted that BMS *never tried* to develop tasimelteon *to treat Non-24.* Tr. 189:9-12 (Polymeropoulos). BMS's purported failures at developing tasimelteon for *other indications*—principally insomnia, which is not a circadian rhythm disorder—are not probative of non-obviousness. *See Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1354 (Fed. Cir. 2016).

Third, Vanda contends that "[t]he CYP3A4 patent succeeded where others failed." Vanda Op. Br. 46 (capitalization omitted). That, too, is wrong. There is no evidence that BMS tried and failed to develop that claimed method. On the

contrary, BMS abandoned its investigation into tasimelteon before performing any in vivo DDI studies. *See* JTX-111.6, 9; *cf. Purdue*, 811 F.3d at 1354.

Even if Vanda had presented any relevant evidence of failures of others—and it has not—it would not be relevant to non-obviousness because the purported failures Vanda identifies occurred in the 1990s and early 2000s. The prior art on which Defendants rely for their obviousness arguments post-date those failures, which renders them "wholly irrelevant" to the obviousness inquiry. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) ("unsuccessful attempts to reach a solution to the problems" addressed by the claimed invention that predate the relevant prior art are "wholly irrelevant").

CONCLUSION

The Court should enter judgment that (i) Defendants do not infringe the asserted claims of the RE604, '829, and '910 patents and (ii) the asserted claims of the patents-in-suit are invalid.

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CERTIFICATE OF COMPLIANCE

I hereby confirm that this document complies with the type and number limitations set forth in the Court's November 6, 2019 Standing Order and the Stipulation and Order Regarding Post-Trial Briefing (D.I. 305). I certify that this document contains 10,936 words, which were counted using the word count feature in Microsoft Word, in 14-point Times New Roman font. The word count does not include the cover page, tables, or the counsel blocks.

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